

## II. REMARKS

### Formal Matters

Claims 2-7, 11, and 12 are pending after entry of the amendments set forth herein.

Claims 2-7, 11, and 12 were examined and were rejected. Claims 8 and 13-15 were withdrawn from consideration.

Claims 2 and 11 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claim 2 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 6, lines 28-30. The amendments to claim 11 are merely editorial in nature. Accordingly, no new matter is added by these amendments.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

### Withdrawal of previous rejections

Applicants note with gratitude that the following rejections, which were made in the Office Action dated September 7, 2001, have not been reiterated and are presumed to have been withdrawn: (1) rejection of claims 1-3, 7, 9, and 10 under 35 U.S.C. §102(b); (2) rejection of claims 1-5, 7, 9, and 10 under 35 U.S.C. §103; and (3) rejection of claims 1-3, 6, 7, 9, and 10 under 35 U.S.C. §103.

### Rejection under 35 U.S.C. §112, first paragraph

Claims 2-7 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

The Office Action stated that the specification does not reasonably provide enablement for making a deletion in the entire range of 15 kb to 3000 kb. Applicants respectfully traverse the rejection.

*The specification provides ample guidance for one of skill in the art to practice the invention without undue experimentation.*

The instant specification provides ample guidance for those skilled in the art to practice the invention as claimed. The specification describes how to make a replacement targeting construct that includes a selectable marker and two regions of sequences that are homologous to the 5' and 3' flanking sequences of the targeted locus; how to introduce such a construct into a host cell; and how to select

cells containing a deletion. Specification, page 6, lines 9-30; and page 8, lines 6-20. The specification provides a working example of the method. Specification, Example 1. The Example describes generation of a 55 kb deletion in a locus. Those skilled in the art, using the instant specification as guidance, could have readily made deletions of sizes other than 55 kb.

*Ramirez-Solis does not support a conclusion of lack of enablement.*

The Office Action stated that Zhang et al. ((1995) *Mol. Cell. Biol.* 14:2404-2410) shows deletions of up to 19.2 kb, and that Zhang stated that a wide spectrum of genomic deletions can be made. The Office Action further stated that Ramirez-Solis et al. ((1995) *Nature* 378:720-724), which published a year and a half later after Zhang, teaches that small deletions (20 kb) have been generated, but that larger deletions have not been possible. However, upon careful reading of Ramirez-Solis, one finds that Ramirez-Solis states, "Small deletions (20 kb) have been generated in embryonic stem (ES) cells by conventional gene targeting, but the constructions of larger deletions, inversions or duplications has not been possible." As a basis for this statement, Ramirez-Solis cites Zhang et al. **Ramirez-Solis did not have access to the instant specification, which was not publicly available on December 14, 1995, when Ramirez-Solis was published.** Ramirez-Solis did not state that it is not possible to generate larger deletions using the method described in the instant specification, as Ramirez-Solis did not have access to the instant specification. Thus, Ramirez-Solis could not have commented on enablement of the instant invention as claimed.

*Others have used the same technique to generate deletions of 100-200 kb.*

The fact that those skilled in the art could generate deletions in the 50 to 3000 kb size range, using the method as claimed, and without undue experimentation, is demonstrated by the fact that others have published results showing that such deletions have been generated using the claimed methods. For example, Kimber et al. ((1999) *Human Molecular Genetics* 8:2229-2237; a copy of which was previously provided) states that replacement-type targeting was used to produce 100-200 kB deletions. Kimber et al., page 2235, column 1, first paragraph under Materials and Methods. Kimber et al. used a targeting construct that included sequences from the 5' and 3' flanking regions of the targeted locus, flanking a sequence encoding neomycin resistance. Kimber et al., page 2231, Figure 1B.

Kimber et al., using the claimed method, generated deletions of approximately 150 kb.

Accordingly, those skilled in the art, given the guidance provided in the instant specification, could readily generate deletions in the recited size range.

The Office Action stated that Kimber used both positive and negative selection; and Kimber used much larger regions of flanking sequences than was described in the instant application. However, the instant application indicates that positive or negative selection can be used. Specification, page 5, lines 19-22. Kimber thus used the procedures as disclosed and claimed in the instant application. Furthermore, the instant application states that the homologous sequences should be at least about 500 bp. Specification, page 6, lines 28-30. Thus, again, Kimber followed the procedures as disclosed and claimed in the instant application.

Applicants submit that the rejection of claims 2-7 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §112, second paragraph

Claims 11 and 12 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

The Office Action stated that claim 11 fails to recite positive process steps which relate to the preamble.

Claim 11 is amended to recite "wherein a mammalian cell deficient in HPRT is obtained."

Applicants submit that the rejection of claims 11 and 12 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

### III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number ABGX001CON3.

Respectfully submitted,  
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